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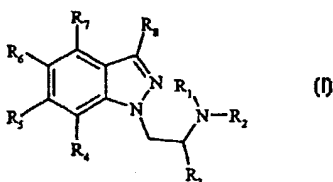


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(54) Title: CHEMICAL COMPOUNDS IV



(57) Abstract

A chemical compound of formula (I) wherein R₁ to R₃ are independently selected from hydrogen and alkyl; R₄ to R₇ are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, amino, monoalkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, arylthio, arylsulfoxyl, arylsulfonyl, alkylsulfoxyl, alkylsulfonyl, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxy carbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino; and R₈ is selected from alkyl and alkoxy, and pharmaceutically acceptable salts and prodrugs thereof, and the use thereof in therapy, particularly for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea, and particularly for the treatment of obesity.

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CHEMICAL COMPOUNDS IV

The present invention relates to indazole derivatives, to processes and intermediates for their preparation, to pharmaceutical compositions containing them and to their medicinal use. The active compounds of the present invention are useful in treating obesity and other disorders.

It has been recognised that obesity is a disease process influenced by environmental factors in which the traditional weight loss methods of dieting and exercise need to be supplemented by therapeutic products (S. Parker, "*Obesity: Trends and Treatments*", Scrip Reports, PJB Publications Ltd, 1996).

Whether someone is classified as overweight or obese is generally determined on the basis of their body mass index (BMI) which is calculated by dividing body weight (kg) by height squared (m^2). Thus, the units of BMI are kg/m^2 and it is possible to calculate the BMI range associated with minimum mortality in each decade of life. Overweight is defined as a BMI in the range 25-30 kg/m^2 , and obesity as a BMI greater than 30 kg/m^2 . There are problems with this definition in that it does not take into account the proportion of body mass that is muscle in relation to fat (adipose tissue). To account for this, obesity can also be defined on the basis of body fat content: greater than 25% and 30% in males and females, respectively.

As the BMI increases there is an increased risk of death from a variety of causes that is independent of other risk factors. The most common diseases with obesity are cardiovascular disease (particularly hypertension), diabetes (obesity aggravates the development of diabetes), gall bladder disease (particularly cancer) and diseases of reproduction. Research has shown that even a modest reduction in body weight can correspond to a significant reduction in the risk of developing coronary heart disease.

Compounds marketed as anti-obesity agents include Orlistat (Reductil®) and Sibutramine. Orlistat (a lipase inhibitor) inhibits fat absorption directly and tends to produce a high incidence of unpleasant (though relatively harmless) side-effects such as diarrhoea. Sibutramine (a mixed 5-HT/noradrenaline reuptake inhibitor) can increase

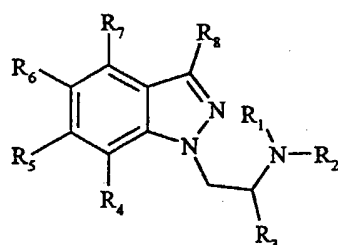
blood pressure and heart rate in some patients. The serotonin releaser/reuptake inhibitors fenfluramine (Pondimin[®]) and dexfenfluramine (Redux[™]) have been reported to decrease food intake and body weight over a prolonged period (greater than 6 months). However, both products were withdrawn after reports of preliminary
5 evidence of heart valve abnormalities associated with their use. There is therefore a need for the development of a safer anti-obesity agent.

The non-selective 5-HT_{2C} receptor agonists/partial agonists m-chlorophenylpiperazine (mCPP) and trifluoromethylphenylpiperazine (TFMPP) have
10 been shown to reduce food intake in rats (G.A. Kennett and G. Curzon, *Psychopharmacol.*, 1988, 96, 93-100; G.A. Kennett, C.T. Dourish and G. Curzon, *Eur. J. Pharmacol.*, 1987, 141, 429-435) and to accelerate the appearance of the behavioural satiety sequence (S.J. Kitchener and C.T. Dourish, *Psychopharmacol.*, 1994, 113, 369-377). Recent findings from studies with mCPP in normal human volunteers and obese
15 subjects have also shown decreases in food intake. Thus, a single dose of mCPP decreased food intake in female volunteers (A.E.S. Walsh *et al.*, *Psychopharmacol.*, 1994, 116, 120-122) and decreased the appetite and body weight of obese male and female subjects during subchronic treatment for a 14 day period (P.A. Sargeant *et al.*, *Psychopharmacol.*, 1997, 133, 309-312). The anorectic action of mCPP is absent in 5-
20 HT_{2C} receptor knockout mutant mice (L.H. Tecott *et al.*, *Nature*, 1995, 374, 542-546) and is antagonised by the 5-HT_{2C} receptor antagonist SB-242084 in rats (G.A. Kennett *et al.*, *Neuropharmacol.*, 1997, 36, 609-620). It seems therefore that mCPP decreases food intake via an agonist action at the 5-HT_{2C} receptor.

25 Other compounds which have been proposed as 5-HT_{2C} receptor agonists for use in the treatment of obesity include the substituted 1-aminoethyl indoles disclosed in EP-A-0655440. CA-2132887 and CA-2153937 disclose that tricyclic 1-aminoethylpyrrole derivatives and tricyclic 1-aminoethyl pyrazole derivatives bind to 5-HT_{2C} receptors and may be used in the treatment of obesity. WO-A-98/30548 discloses aminoalkylindazole
30 compounds as 5-HT_{2C} agonists for the treatment of CNS diseases and appetite regulation disorders.

It is an object of this invention to provide selective, directly acting 5HT₂ receptor ligands for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide directly acting ligands selective for 5-HT_{2B} and/or 5-HT_{2C} receptors, for use in therapy and particularly for use as anti-obesity agents. It is a further object of this invention to provide selective, directly acting 5-HT_{2C} receptor ligands, preferably 5-HT_{2C} receptor agonists, for use in therapy and particularly for use as anti-obesity agents.

According to the present invention there is provided a chemical compound of formula (I):



(I)

wherein:

- 15 R₁ to R₃ are independently selected from hydrogen and alkyl;
 R₄ to R₇ are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, amino, monoalkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, arylthio, arylsulfoxyl, arylsulfonyl, alkylsulfoxyl, alkylsulfonyl, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl,
 20 dialkylaminocarbonyl, alkoxy carbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino; and
 R₈ is selected from alkyl and alkoxy,
 and pharmaceutically acceptable salts and prodrugs thereof.

25

As used herein, the term "alkyl" means a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical. Where cyclic, the alkyl group is preferably C₃ to C₁₂, more preferably C₅ to C₁₀, more preferably C₅, C₆ or C₇. Where acyclic, the alkyl group is preferably C₁ to C₁₀, more preferably C₁ to

C₆, more preferably methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl), more preferably methyl.

As used herein, the term "lower alkyl" means methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl).

As used herein, the term "aryl" means an aromatic group, such as phenyl or naphthyl, or a heteroaromatic group containing one or more, preferably one, heteroatom, such as pyridyl, pyrrolyl, furanyl and thienyl.

The alkyl and aryl groups may be substituted or unsubstituted. Where substituted, there will generally be 1 to 3 substituents present, preferably 1 substituent. Substituents may include:

carbon-containing groups such as

alkyl,
aryl,
arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl);

halogen atoms and halogen-containing groups such as

haloalkyl (e.g. trifluoromethyl);

oxygen-containing groups such as

alcohols (e.g. hydroxy, hydroxyalkyl, aryl(hydroxy)alkyl),
ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl),
aldehydes (e.g. carboxaldehyde),
ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl, arylcarbonyl, arylalkylcarbonyl, arylcarbonylalkyl),
acids (e.g. carboxy, carboxyalkyl),
acid derivatives such as esters
(e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl),
amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono-

- or di-alkylaminocarbonylalkyl,
arylamino-carbonyl),
carbamates (e.g. alkoxycarbonylamino,
aryloxycarbonylamino, aminocarbonyloxy, mono-
5 or di-alkylaminocarbonyloxy,
arylamino-carbonyloxy)
and ureas (e.g. mono- or di-alkylaminocarbonylamino or
arylamino-carbonylamino);
nitrogen-containing groups such as
10 amines (e.g. amino, mono- or di-alkylamino, aminoalkyl,
mono- or di-alkylaminoalkyl),
azides,
nitriles (e.g. cyano, cyanoalkyl),
nitro;
15 sulfur-containing groups such as
thiols, thioethers, sulfoxides and sulfones
(e.g. alkylthio, alkylsulfinyl, alkylsulfonyl,
alkylthioalkyl, alkylsulfinylalkyl,
alkylsulfonylalkyl, arylthio, arylsulfinyl,
20 arylsulfonyl, arylthioalkyl, arylsulfinylalkyl,
arylsulfonylalkyl);
and heterocyclic groups containing one or more, preferably one, heteroatom,
(e.g. thienyl, furanyl, pyrrolyl, imidazolyl,
pyrazolyl, thiazolyl, isothiazolyl, oxazolyl,
25 oxadiazolyl, thiadiazolyl, aziridiny, azetidiny,
pyrrolidiny, pyrroliny, imidazolidiny,
imidazolinyl, pyrazolidiny, tetrahydrofuranyl,
pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl,
piperidyl, hexahydroazepiny, piperazinyl,
30 morpholinyl, thianaphthyl, benzofuranyl,
isobenzofuranyl, indolyl, oxyindolyl, isoindolyl,
indazolyl, indolinyl, 7-azaindolyl, benzopyranyl,
coumarinyl, isocoumarinyl, quinolinyl,

isoquinolinyl, naphthridinyl, cinnolinyl,
quinazolinyl, pyridopyridyl, benzoxazinyl,
quinoxalinyl, chromenyl, chromanyl,
isochromanyl, phthalazinyl and carbolinyl).

5

As used herein, the term "alkoxy" means alkyl-O- and "alkoyl" means alkyl-CO-. Alkoxy substituent groups or alkoxy-containing substituent groups may be substituted by one or more alkyl groups.

10

As used herein, the term "halogen" means a fluorine, chlorine, bromine or iodine radical, preferably a fluorine, chlorine or bromine radical, and more preferably a fluorine or chlorine radical.

15

As used herein the term "prodrug" means any pharmaceutically acceptable prodrug of the compound of formula (I).

20

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are fumaric, hydrochloric, hydrobromic, succinic, phosphoric, sulfuric and methanesulfonic acids.

25

Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminium salts.

Preferably, the compounds of formula (I) are selected from compounds in which R_1 is the same as R_2 . Preferably, R_1 and R_2 are both hydrogen.

30

In an embodiment of the present invention, R_1 is hydrogen and R_2 is alkyl, preferably lower alkyl, preferably methyl. In a further embodiment, R_1 is hydrogen and R_2

is arylalkyl, preferably arylmethyl. Where R_2 is arylalkyl, it is preferred that said aryl substituent is a substituted or unsubstituted phenyl or thienyl group.

Preferably, the compounds of formula (I) are selected from compounds in which
5 R_3 is alkyl, preferably lower alkyl, preferably methyl. Where R_3 is alkyl, the carbon atom to which R_3 is attached is an asymmetric carbon atom. It is preferred that this asymmetric carbon is in the (*S*)-configuration, wherein the stereochemical assignment is defined with respect to a compound wherein R_3 is an unsubstituted alkyl group.

10 R_4 to R_7 are independently selected from hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, amino, monoalkylamino, dialkylamino, alkoxy (including arylalkoxy), aryloxy, alkylthio, arylthio, arylsulfoxyl, arylsulfonyl, alkylsulfoxyl, alkylsulfonyl, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl,
15 dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino.

In one embodiment of the invention R_4 to R_7 are independently selected from
20 hydrogen, halogen, hydroxy, alkyl (including cycloalkyl, halo-alkyl (such as trifluoromethyl) and arylalkyl), aryl, alkoxy (including arylalkoxy), aryloxy, alkylthio, alkylsulfoxyl and alkylsulfonyl.

Preferably, the compounds of formula (I) are selected from compounds in which
25 one or more of R_4 , R_5 , R_6 and R_7 is/are hydrogen. Preferably, one or both of R_4 and R_7 are hydrogen.

In a preferred embodiment of the invention, one or more, preferably one or two, of
 R_4 , R_5 , R_6 and R_7 are selected from halogen, preferably fluoro, chloro and bromo.
30 Preferably one or both of R_5 and R_6 are selected from halogen.

In an alternative preferred embodiment, R₅ is selected from halogen, alkoxy (preferably lower alkoxy), alkylthio (preferably lower alkylthio) and alkyl (preferably trifluoromethyl).

5 In a further alternative preferred embodiment, R₆ is selected from hydrogen and halogen (preferably fluoro).

Preferably, the compounds of formula (I) are selected from compounds in which R₈ is alkyl, preferably methyl or ethyl, more preferably ethyl.

10

In a preferred embodiment of the invention, the compounds of formula (I) are selected from 1-(6-methoxy-3-methylindazol-1-yl)-2-propylamine, 1-(5,6-difluoro-3-methylindazol-1-yl)-2-propylamine, 1-(6-chloro-5-fluoro-3-methylindazol-1-yl)-2-propylamine, 1-(3-ethyl-6-trifluoromethylindazol-1-yl)-2-propylamine, 1-(6-bromo-3-ethylindazol-1-yl)-2-propylamine and 1-(3-ethyl-6-methylthioindazol-1-yl)-2-propylamine. 1-(3-Ethyl-6-methylthioindazol-1-yl)-2-propylamine and 1-(6-bromo-3-ethylindazol-1-yl)-2-propylamine are particularly preferred. It is preferred that the compounds are the (*S*)-enantiomers thereof. Where the compounds of formula (I) are in salt form, the fumarate salt is particularly preferred.

20

The compounds of the invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. The compounds can be, for example, racemates or optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

25

In a preferred embodiment of the invention, a compound of formula (I) is in the form of its (*S*)-enantiomer, substantially free of its (*R*)-enantiomer. As used herein, the term "substantially free of its (*R*)-enantiomer" means that a composition comprising a compound of formula (I) contains a greater proportion of the (*S*)-enantiomer of the compound of formula (I) in relation to the (*R*)-enantiomer of the compound of formula (I). In a preferred embodiment of the present invention, the term "substantially free of its (*R*)-enantiomer", as used herein, means that the composition contains at least 90 % by weight of the (*S*)-enantiomer and 10 % by weight or less of the (*R*)-enantiomer. In a

30

further preferred embodiment, the term "substantially free of its (*R*)-enantiomer" means that the composition contains at least 99 % by weight of the (*S*)-enantiomer and 1 % or less of the (*R*)-enantiomer. In another preferred embodiment, the term "substantially free of its (*R*)-enantiomer" means that the composition contains 100 % by weight of the (*S*)-enantiomer. The above percentages are based on the total amount of a compound of formula (I) present in the composition.

According to a further aspect of the invention, there is provided a compound of formula (I) for use in therapy.

10

The compounds of formula (I) may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT₂ receptor function. The compounds may act as receptor agonists or antagonists. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders associated with 5-HT_{2B} and/or 5-HT_{2C} receptor function. Preferably, the compounds may be used in the treatment (including prophylactic treatment) of disorders where a 5-HT_{2C} receptor agonist is required.

The compounds of formula (I) may be used in the treatment or prevention of central nervous disorders such as depression, atypical depression, bipolar disorders, anxiety disorders, obsessive-compulsive disorders, social phobias or panic states, sleep disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other conditions associated with cephalic pain or other pain, raised intracranial pressure, epilepsy, personality disorders, age-related behavioural disorders, behavioural disorders associated with dementia, organic mental disorders, mental disorders in childhood, aggressivity, age-related memory disorders, chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia nervosa or premenstrual tension; damage of the central nervous system such as by trauma, stroke, neurodegenerative diseases or toxic or infective CNS diseases such as encephalitis or meningitis; cardiovascular disorders such as thrombosis; gastrointestinal disorders such as dysfunction of gastrointestinal motility; diabetes insipidus; and sleep apnea.

According to a further aspect of the invention, there is provided use of a compound of formula (I) in the manufacture of a medicament for the treatment (including prophylaxis) of the above-mentioned disorders. In a preferred embodiment, there is provided use of a compound of formula (I) in the manufacture of a medicament
5 for the treatment (including prophylaxis) of obesity.

According to a further aspect of the invention, there is provided a method of treatment (including prophylaxis) of a disorder selected from the group consisting of the above-mentioned disorders comprising administering to a patient in need of such
10 treatment an effective dose of a compound of formula (I). In a preferred embodiment, there is provided a method of treatment (including prophylaxis) of obesity.

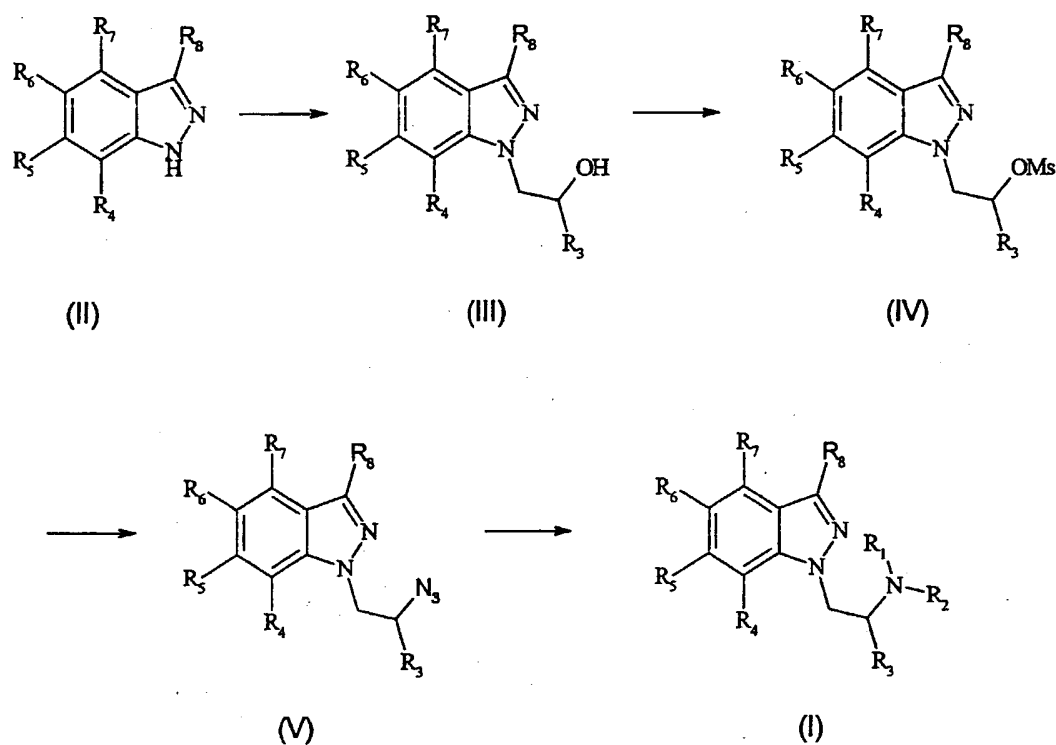
According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) in combination with
15 a pharmaceutically acceptable carrier or excipient and a method of making such a composition comprising combining a compound of formula (I) with a pharmaceutically acceptable carrier or excipient.

According to a further aspect of the invention, there is provided a method of
20 preparing a compound of formula (I).

Compounds of the invention may be prepared according to Reaction Scheme 1. R_1 to R_8 are as previously defined. The (indazolyl)-alkylethanol (III) may be prepared by reaction of the substituted indazole (II) with an alkylene oxide in the presence of a
25 strong base such as sodium hydride in a solvent such as tetrahydrofuran. The corresponding azido derivative (V) can be formed in a two step procedure from the derivative (III) by formation of the mesylate (IV), obtained by reaction of (III) with methanesulfonyl chloride in the presence of a base such as triethylamine, and subsequent treatment of the mesylate (IV) with sodium azide in a solvent such as
30 dimethyl formamide. The azidoindazole (V) can then be reduced to a compound of formula (I) ($R_1 = R_2 = H$) using for example a mixture of zinc powder and nickel chloride hexahydrate in a solvent such as tetrahydrofuran. The compounds of formula (I) (R_1 and/or $R_2 = \text{alkyl}$) may be prepared by standard methods such as reductive

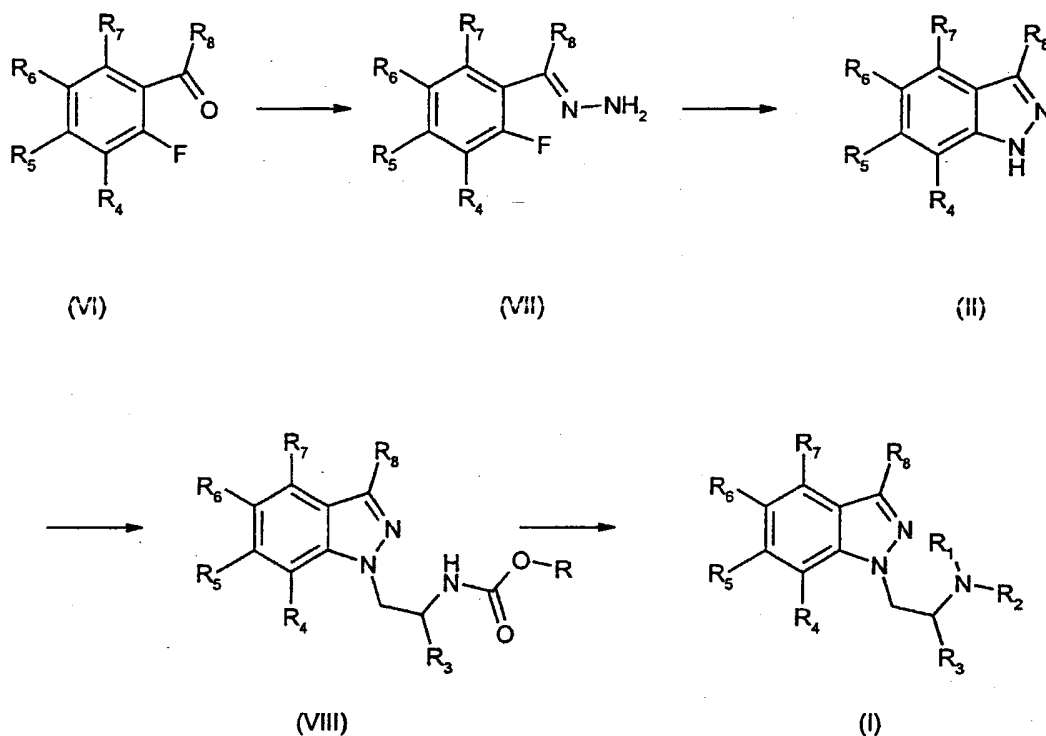
alkylation of compound (I) ($R_1 = R_2 = H$) with an appropriate aldehyde or ketone in the presence of a reducing agent such as sodium triacetoxyborohydride, formic acid or sodium cyanoborohydride.

5 Reaction Scheme 1



Alternatively, compounds of the invention may be prepared according to Reaction Scheme 2. R_1 to R_8 are as previously defined. The hydrazone (VII) may be prepared by reaction of the alkyl-aryl ketone (VI) with hydrazine. The indazole (II) can be formed from the hydrazone (VII) by thermally-induced cyclisation with elimination of hydrogen fluoride. The carbamate (VIII) may be formed by reaction of the indazole (II) with a 2-carbamylethylsulfonate in the presence of a strong base such as potassium hydroxide in a solvent such as methyl sulfoxide. The indazole-2-alkylamine (I) ($R_1 = R_2 = H$) may be obtained by reaction of the carbamate (VIII) with a reagent suitable to reveal the protected amine function.

Reaction Scheme 2



5

If, in any of the other processes mentioned herein, the substituent group R_4 , R_5 , R_6 , R_7 or R_8 is other than the one required, the substituent group may be converted to the desired substituent by known methods. The substituents R_4 , R_5 , R_6 , R_7 or R_8 may also need protecting against the conditions under which the reaction is carried out. In such a case, the protecting group may be removed after the reaction has been completed.

The processes described above may be carried out to give a compound of the invention in the form of a free base or as an acid addition salt. If the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid addition salt. Conversely, if the product of the process is a free base, an acid addition salt, particularly a pharmaceutically acceptable acid addition salt, may be obtained by dissolving the free base in a suitable organic solvent and treating

the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from basic compounds.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. Thus, the active compounds of the invention may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) transdermal or rectal administration or in a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulfate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid).

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The active compounds of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles,

and may contain formulating agents such as suspending, stabilizing and/or dispersing agents.

Alternatively, the active ingredient may be in powder form for reconstitution
5 with a suitable vehicle, *e.g.* sterile pyrogen-free water, before use.

The active compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, *e.g.*, containing conventional suppository bases such as cocoa butter or other glycerides.

10

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use
15 of a suitable propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from
20 gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

A proposed dose of the active compounds of the invention for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions
25 referred to above (*e.g.*, obesity) is 0.1 to 500 mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

The invention will now be described in detail with reference to the following examples. It will be appreciated that the invention is described by way of example only
30 and modification of detail may be made without departing from the scope of the invention.

EXPERIMENTAL

Assay Procedures

5 1. Binding to serotonin receptors

The binding of compounds of formula I to serotonin receptors was determined *in vitro* by standard methods. The preparations were investigated in accordance with the assays given hereinafter.

10 Method (a): For the binding to the 5-HT_{2c} receptor the 5-HT_{2c} receptors were radiolabeled with [³H]-5-HT. The affinity of the compounds for 5-HT_{2c} receptors in a CHO cell line was determined according to the procedure of D. Hoyer, G. Engel and H.O. Kalkman, *European J. Pharmacol.*, 1985, 118, 13-23.

15 Method (b): For the binding to the 5-HT_{2B} receptor the 5-HT_{2B} receptors were radiolabeled with [³H]-5-HT. The affinity of the compounds for human 5-HT_{2B} receptors in a CHO cell line was determined according to the procedure of K. Schmuck, C. Ullmer, P. Engels and H. Lubbert, *FEBS Lett.*, 1994, 342, 85-90.

20 The thus determined activity of compounds of formula (I) is shown in Table 1.

Table 1

Compound	Method (a)	Method (b)
	K _i (2C)	K _i (2B)
Example 1	431 nM	241 nM
Example 2	210 nM	135 nM
Example 3	140 nM	63 nM
Example 4	75 nM	26 nM
Example 8	37 nM	47 nM

2. Functional activity

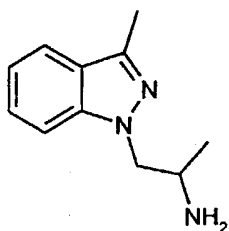
25 The functional activity of compounds of formula (I) was assayed using a Fluorimetric Imaging Plate reader (FLIPR). CHO cells expressing the human 5-HT_{2C} or

human 5-HT_{2A} receptors were counted and plated into standard 96 well microtitre plates on the day before testing to give a confluent monolayer. The cells were then dye loaded with the calcium sensitive dye, Fluo-3-AM. Unincorporated dye was removed using an automated cell washer to leave a total volume of 100 µL/well of assay buffer (Hanks
5 balanced salt solution containing 20 mM Hepes and 2.5 mM probenecid). The drug (dissolved in 50 µL of the assay buffer) was added at a rate of 70 µL/sec to each well of the FLIPR 96 well plate during fluorescence measurements. The measurements were taken at 1 sec intervals and the maximum fluorescent signal was measured (approx 10-15 secs after drug addition) and compared with the response produced by 10 µM 5-HT
10 (defined as 100%) to which it was expressed as a percentage response (relative efficacy). Dose response curves were constructed using Graphpad Prism (Graph Software Inc.).

The thus determined activity of compounds of formula (I) is shown in Table 2.

Table 2

Compound	h5-HT _{2A}		h5-HT _{2C}	
	EC ₅₀ (nM)	Relative Efficacy (%)	EC ₅₀ (nM)	Relative Efficacy (%)
Example 1	-	-	960	55
Example 2	108	59	44	74
Example 3	152	50	84	67
Example 4	137	65	48	76
Example 5	-	-	877	73
Example 6	288	32	52	47
Example 7	739	39	88	69
Example 8	285	48	8	81

Synthetic Examples5 **Example 1:** (*RS*)-1-(3-Methylindazol-1-yl)-2-propylamine fumarate*(RS)*-1-[2-(tert-Butoxycarbonylamino)propyl]-3-methylindazole

10

3-Methyl-1*H*-indazole (1.0 g, 7.6 mmol) was added portionwise to a stirred mixture of methyl sulfoxide (25 mL) and powdered potassium hydroxide (85%, 1.5 g, 26.6 mmol). The mixture was warmed to 35 °C and left to stir for 30 min. A mixture of (*RS*)-2-(tert-butoxycarbonylamino)propane methanesulfonate (4.9 g, 19.4 mmol) in methyl sulfoxide (10 mL) was added over 2 h, the mixture was then left to stir at 35 °C for 20 h. Water (20 mL) was added and the mixture was extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (2 x), dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO₂; heptane-ethyl acetate (5:1)] to give the product (1.2 g, 51% yield) as a pale yellow solid: IR ν_{\max}

(Nujol/cm⁻¹) 3368, 1683, 1536, 1461, 1370, 1249, 1170, 1059, and 743; NMR δ_H (400 MHz, CDCl₃) 1.13 (3H, d, *J* 6.5 Hz), 1.41 (9H, s), 2.57 (3H, s), 4.11 (1H, m), 4.28-4.48 (2H, m), 4.85 (1H, br s), 7.08-7.14 (1H, m), 7.33-7.46 (2H, m) and 7.64 (1H, d, *J* 8 Hz).

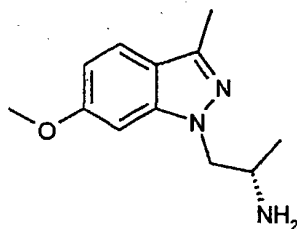
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(*RS*)-1-(3-Methylindazol-1-yl)-2-propylamine fumarate

A mixture of (*RS*)-1-[2-(tert-butoxycarbonylamino)propyl]-3-methylindazole (1.2 g, 4.3 mmol), dichloromethane (15 mL) and trifluoroacetic acid (5 mL) was stirred
10 for 1 h. The mixture was partitioned between aqueous sodium hydroxide solution (2 N, 30 mL) and dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine (2 x), dried (magnesium sulfate) and concentrated *in vacuo* to give an orange oil. 2-Propanol (5 mL) was added, the mixture was heated to boiling, then fumaric acid (0.5 g, 4.3 mmol) was added. The mixture was cooled to room temperature and filtered.
15 The filter cake was dried *in vacuo* to give the title compound (0.89 g, 68%) as a pale brown solid: mp 145-147 °C; IR ν_{max} (Nujol/cm⁻¹) 1618, 1510, 1458, 1377, 973, 742 and 652; NMR δ_H (400 MHz, DMSO-*d*₆) 1.09 (3H, d, *J* 6.5 Hz), 2.49 (3H, s), 3.56 (1H, m), 4.39 (2H, m), 6.47, (2H, s), 7.09-7.15 (1H, m), 7.36-7.41 (1H, m), 7.62 (1H, d, *J* 8 Hz) and 7.72 (1H, d, *J* 8 Hz).

20

Example 2: (*S*)-1-(6-Methoxy-3-methylindazol-1-yl)-2-propylamine fumarate

25 6-Methoxy-3-methyl-1*H*-indazole

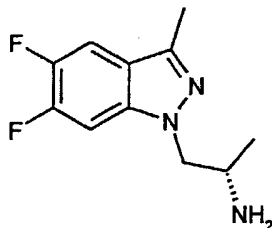
To a stirred solution of 2'-fluoro-4'-methoxyacetophenone (0.5 g, 3.0 mmol) in ethylene glycol (10 mL) was added dropwise hydrazine hydrate (0.1 g, 3.1 mmol). The mixture was stirred for 24 h and partitioned between dichloromethane (20 mL) and water (3 x 20 mL). The organic layer was dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO₂; ethyl acetate-heptane (1:1)] to give an orange oil. The oil was dissolved in ethylene glycol (10 mL) and heated at 165 °C for 24 h. The solution was cooled to room temperature and partitioned between dichloromethane (20 mL) and water (3 x 20 mL). The organic extract was dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO₂; ethyl acetate-heptane (1:5)] to give the product (0.25 g, 51%) as a colourless solid: IR ν_{\max} (Nujol/cm⁻¹) 1624, 1519, 1458, 1295, 1208, 1170, 1024 and 821; NMR δ_{H} (400 MHz, CDCl₃) 2.54 (3H, s), 3.86 (3H, s), 6.78-6.81 (2H, m) and 7.52 (1H, d, *J* 9 Hz).

15 (S)-1-[2-(tert-Butoxycarbonylamino)propyl]-6-methoxy-3-methylindazole

(S)-1-[2-(tert-Butoxycarbonylamino)propyl]-6-methoxy-3-methylindazole was prepared from 6-methoxy-3-methyl-1*H*-indazole (0.19 g, 1.1 mmol) and (S)-2-(tert-butoxycarbonylamino)propane methanesulfonate according to the method described in Example 1 to give the product (0.18 g, 51% yield) as a pale orange oil: NMR δ_{H} (400 MHz, CDCl₃) 1.13 (3H, d, *J* 6.5 Hz), 1.41 (9H, s), 2.52 (3H, s), 3.89 (3H, s), 4.12 (1H, m), 4.26 (H, m), 4.31-4.41 (1H, m), 4.96 (1H, br s), 6.76 (1H, dd, *J* 2 Hz, *J* 6.5 Hz), 6.78-6.83 (1H, m) and 7.48 (1H, d, *J* 9 Hz).

25 (S)-1-(6-Methoxy-3-methylindazol-1-yl)-2-propylamine fumarate

(S)-1-(6-Methoxy-3-methylindazol-1-yl)-2-propylamine fumarate was prepared from (S)-1-[2-(tert-butoxycarbonylamino)propyl]-6-methoxy-3-methylindazole according to the method described in Example 1 to give the title compound (0.071 g, 62%) as a white solid: mp 180-181 °C; Found C, 56.96; H, 6.36; N, 12.45%. C₁₂H₁₇N₃O.C₄H₄O₄ requires: C, 57.30; H, 6.31; N, 12.52%; NMR δ_{H} (400 MHz, DMSO-*d*₆) 1.16 (3H, d, *J* 6.5 Hz), 2.44 (3H, s), 3.63 (1H, m), 3.85 (3H, s), 4.38 (1H, dd, *J* 14, 6.5 Hz), 4.51 (1H, dd, *J* 14, 6.5 Hz), 6.49, (2H, s), 6.74 (1H, m), 7.19 (1H, m) and 7.52 (1H, d, *J* 8.5 Hz)

Example 3: (S)-1-(5,6-Difluoro-3-methylindazol-1-yl)-2-propylamine fumarate

5

5,6-Difluoro-3-methyl-1H-indazole

5,6-Difluoro-3-methyl-1H-indazole was prepared according to the method described in Example 2 using 2',4',5'-trifluoroacetophenone (1.0 g, 5.7 mmol) to produce 0.44 g (48% yield) of the product as a white solid: IR ν_{\max} (Nujol/cm⁻¹) 1642, 1513, 1461, 1377, 1336, 1202, 1055 and 848; NMR δ_{H} (400 MHz, CDCl₃) 2.55 (3H, s), 7.19 (1H, dd, *J* 4, 6 Hz) and 7.39 (1H, dd, *J* 2, 7.5 Hz).

15

(S)-1-[2-(tert-Butoxycarbonylamino)propyl]-5,6-difluoro-3-methylindazole

(S)-1-[2-(tert-Butoxycarbonylamino)propyl]-5,6-difluoro-3-methylindazole was prepared according to the method described in Example 2 using 5,6-difluoro-3-methyl-1H-indazole (0.26 g, 1.6 mmol) to produce 0.28 g (57% yield) of the product as a white solid: NMR δ_{H} (400 MHz, CDCl₃) 1.13 (3H, d, *J* 6.5 Hz), 1.42 (9H, s), 2.51 (3H, s), 4.03 (1H, m), 4.26-4.4 (2H, m), 4.67 (1H, br s), 7.17-7.26 (1H, m) and 7.31-7.38 (1H, m).

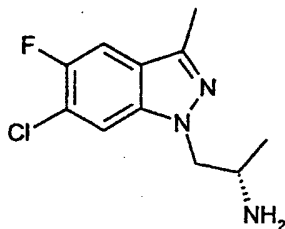
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(S)-1-(5,6-Difluoro-3-methylindazol-1-yl)-2-propylamine fumarate

(S)-1-(5,6-Difluoro-3-methylindazol-1-yl)-2-propylamine fumarate was prepared according to the method described in Example 2 using (S)-1-[2-(tert-butoxycarbonylamino)propyl]-5,6-difluoro-3-methylindazole (0.28 g, 0.9 mmol) to

produce 0.16 g (51% yield) of the title compound as a white solid: mp 160-161 °C; Found C, 51.81; H, 4.94; N, 11.85%. $C_{11}H_{13}F_2N_3 \cdot C_4H_4O_4 \cdot 0.25H_2O$ requires: C, 52.10; H, 5.10; N, 12.15%; IR ν_{\max} (Nujol/ cm^{-1}) 1713, 1632, 1518, 1457, 1377, 972 and 848; NMR δ_H (400 MHz, DMSO- d_6) 1.13 (3H, d, J 6 Hz), 2.48 (3H, s), 3.51-3.62 (1H, m), 4.32-4.5 (2H, m), 6.51 (2H, s) and 7.79-7.89 (2H, m).

Example 4: (*S*)-1-(6-Chloro-5-fluoro-3-methylindazol-1-yl)-2-propylamine fumarate



10

6-Chloro-5-fluoro-3-methyl-1*H*-indazole

6-Chloro-5-fluoro-3-methyl-1*H*-indazole was prepared according to the method described in Example 2 using 4'-chloro-2',5'-difluoroacetophenone (2.0 g, 10 mmol) to produce 0.83 g (45% yield) of the product as a beige solid: IR ν_{\max} (Nujol/ cm^{-1}) 3221, 1457, 1306, 1294, 1071, 1012 and 856; NMR δ_H (400 MHz, CDCl_3) 2.54 (3H, s), 7.39 (1H, d, J 9 Hz) and 7.49 (1H, d, J 5.5 Hz).

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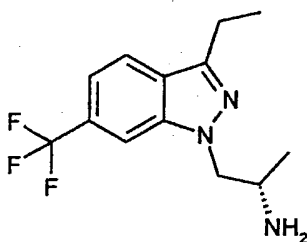
(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-6-chloro-5-fluoro-3-methylindazole

(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-6-chloro-5-fluoro-3-methylindazole was prepared according to the method described in Example 2 using 6-chloro-5-fluoro-3-methyl-1*H*-indazole (0.27 g, 1.5mmol) to produce 0.28 g (62%) of the product as a beige solid: IR ν_{\max} (Nujol/ cm^{-1}) 3361, 1678, 1532, 1461, 1238, 1165, 1082, 860 and 638; NMR δ_H (400 MHz, CDCl_3) 1.16 (3H, d, J 6.5Hz), 1.41 (9H, s), 2.52 (3H, s), 4.05 (1H, m), 4.28-4.41 (2H, m), 4.66 (1H, br s), 7.33 (1H, d, J 9 Hz) and 7.45-7.5 (1H, m).

(*S*)-1-(6-Chloro-5-fluoro-3-methylindazol-1-yl)-2-propylamine fumarate

(*S*)-1-(6-Chloro-5-fluoro-3-methylindazol-1-yl)-2-propylamine fumarate was prepared according to the method described in Example 2 using (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-6-chloro-5-fluoro-3-methylindazole (0.28 g, 0.9 mmol) to produce 0.19 g (61% yield) of the title compound as a white solid: mp 158-159 °C; Found C, 50.07; H, 4.75; N, 11.43%. $C_{11}H_{13}ClFN_3 \cdot C_4H_4O_4$ requires: C, 50.36; H, 4.79; N, 11.74%; IR ν_{max} (Nujol/cm⁻¹) 1713, 1626, 1512, 1458, 1241, 975, 816 and 651; NMR δ_H (400 MHz, DMSO-*d*₆) 1.13 (3H, d, *J* 6 Hz), 2.49 (3H, s), 3.49-3.61 (1H, m), 4.33-4.52 (2H, m), 6.49 (2H, s) and 7.81 (1H, d, *J* 9.5 Hz) and 8.07 (1H, d, *J* 6 Hz).

Example 5: (*S*)-1-(3-Ethyl-6-trifluoromethylindazol-1-yl)-2-propylamine fumarate



2'-Fluoro-4'-trifluoromethylphenylpropiohydrazone

To a stirred solution of 2'-fluoro-4'-trifluoromethylpropiophenone (2.0 g, 9 mmol) in ethylene glycol (20 mL) was added dropwise hydrazine hydrate (0.58 g, 0.9 mmol). The mixture was stirred for 24 h and partitioned between dichloromethane (40 mL) and water (3 x 20 mL). The organic layer was dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO₂; ethyl acetate-heptane (1:5)] to give the product (1.3 g, 61%) as a colourless oil: IR ν_{max} (Nujol/cm⁻¹) 3388, 1421, 1330, 1172, 1130, 900 and 746; NMR δ_H (400 MHz, CDCl₃) 1.10 (3H, t, *J* 7 Hz), 2.51 (0.6H, q, *J* 7.5 Hz), 2.61 (1.4H, q, 7.5 Hz), 5.06 (0.6H, br s), 5.59 (1.4H, br s), 7.29-7.55 (2.2H, m) and 7.61 (0.8H, t, *J* 8.5 Hz).

3-Ethyl-6-trifluoromethyl-1*H*-indazole

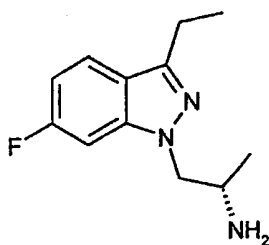
A solution of 2'-fluoro-4'-trifluoromethylphenylpropiohydrazone (1.3 g, 5.6 mmol) in ethylene glycol (50 mL) was heated at 165 °C for 24 h. The solution was cooled to room temperature and partitioned between dichloromethane (70 mL) and the solution
5 water (3 x 20 mL). The organic layer was dried (magnesium sulfate), concentrated *in vacuo* and purified by column chromatography [SiO₂; ethyl acetate-heptane (1:5)] to give the product (0.5 g, 41%) as a yellow solid: IR ν_{\max} (Nujol/cm⁻¹) 3265, 1467, 1455, 1338, 1235, 1115, 874 and 714; NMR δ_{H} (400 MHz, CDCl₃) 1.45 (3H, t, *J* 8 Hz), 3.07
10 (2H, q, *J* 7.5 Hz), 7.37 (1H, d, *J* 8.5 Hz), 7.75 (1H, s), 7.83 (1H, d, *J* 8.5 Hz) and 9.75 (1H, br s).

(S)-1-[2-(tert-Butoxycarbonylamino)propyl]-3-ethyl-6-trifluoromethylindazole

15 *(S)*-1-[2-(tert-Butoxycarbonylamino)propyl]-3-ethyl-6-trifluoromethylindazole was prepared according to the method described in Example 2 using 3-ethyl-6-trifluoromethylindazole (0.49 g, 2.3 mmol) to produce 0.48 g (56%) of the product as a white solid: IR ν_{\max} (Nujol/cm⁻¹) 3360, 1681, 1531, 1461, 1313, 1169, and 1120; NMR δ_{H} (400 MHz, CDCl₃) 1.16 (3H, d, *J* 6.5 Hz), 1.33-1.43 (12H, m), 3.01 (2H, q, *J* 7 Hz),
20 4.07-4.18 (1H, m), 4.39-4.49 (2H, m), 4.76 (1H, br s), 7.32 (1H, d, *J* 8 Hz) 7.71 (1H, br s) and 7.78 (1H, d, *J* 8.5 Hz).

(S)-1-(3-Ethyl-6-trifluoromethylindazol-1-yl)-2-propylamine fumarate

25 *(S)*-1-(3-Ethyl-6-trifluoromethylindazol-1-yl)-2-propylamine fumarate was prepared according to the method described in Example 2 using *(S)*-1-[2-(tert-butoxycarbonylamino)propyl]-3-ethyl-6-trifluoromethylindazole (0.3 g, 0.8 mmol) to produce 0.20 g (63% yield) of the title compound as a white solid: mp 151-153 °C; Found C, 52.34; H, 5.27; N, 10.62%. C₁₁H₁₃F₃N₃·C₄H₄O₄ requires: C, 52.71; H, 5.20;
30 N, 10.85%; IR ν_{\max} (Nujol/cm⁻¹) 1707, 1630, 1501, 1461, 1376, 1313, 1124, 1059 and 652; NMR δ_{H} (400 MHz, DMSO-*d*₆) 1.17 (3H, d, *J* 7 Hz), 1.35 (3H, t, *J* 7 Hz), 2.99 (2H, q, *J* 7.5 Hz), 3.62 (1H, m), 4.48-4.56 (1H, m), 4.59-4.68 (1H, m), 6.49 (2H, s), 7.4 (1H, d, *J* 8.5 Hz), 8.01 (1H, d, *J* 8.5 Hz) and 8.22 (1H, s).

Example 6: (S)-1-(3-Ethyl-6-fluoroindazol-1-yl)-2-propylamine fumarate

5

2',4'-Difluorophenylpropiohydrazone

2',4'-Difluorophenylpropiohydrazone was prepared according to the method described in Example 5 using 2',4'-difluoropropiophenone (5.0 g, 30 mmol) to produce 2.6 g (48%) of the product as a colourless oil: IR ν_{\max} (Nujol/cm⁻¹) 3385, 1614, 1502, 1420, 1267, 1140, 968 and 850; NMR δ_{H} (400 MHz, CDCl₃) 1.03-1.15 (3H, m), 2.48 (0.7H, q, *J* 7.5 Hz), 2.58 (1.3H, q, *J* 7.5 Hz), 5.04 (0.7H, br s), 5.46 (1.3H, br s), 6.76-7.01 (2H, m), 7.16-7.23 (0.4H, m) and 7.4-7.47 (0.6H, m).

15

3-Ethyl-6-fluoro-1*H*-indazole

3-Ethyl-6-fluoro-1*H*-indazole was prepared according to the method described in Example 5 using 2',4'-difluorophenylpropiohydrazone (3.5 g, 19 mmol) to produce 1.7 g (53%) of the product as a white solid: IR ν_{\max} (Nujol/cm⁻¹) 3168, 1633, 1350, 1230, 1153, 1124, 1041 and 838; NMR δ_{H} (400 MHz, CDCl₃) 1.42 (3H, t, *J* 7.5 Hz), 3.01 (2H, q, *J* 8 Hz), 6.91 (1H, m), 7.08 (1H, dd, *J* 2, 9.5 Hz), 7.65 (1H, dd, *J* 5.5, 9 Hz) and 9.12 (1H, br s).

25 **(S)-1-[2-(tert-Butoxycarbonylamino)propyl]-3-ethyl-6-fluoroindazole**

(*S*)-1-[2-(tert-Butoxycarbonylamino)propyl]-3-ethyl-6-fluoroindazole was prepared according to the method described in Example 2 using 3-ethyl-6-fluoro-1*H*-indazole (1.5 g, 9 mmol) to produce 1.47 g (51%) of the product as a white solid: IR ν_{\max} (Nujol/cm⁻¹), 3363, 1677, 1534, 1463, 1368, 1267, 1161, 1066 and 844; NMR δ_{H} (400 MHz, CDCl₃) 1.15 (3H, d, *J* 7 Hz), 1.34-1.44 (12H, m), 2.96 (2H, q, *J* 7.5 Hz), 4.06 (1H, m), 4.31-4.37 (2H, m), 4.79 (1H, br s), 6.87 (1H, m), 7.06 (1H, d, *J* 9.5 Hz) and 7.59 (1H, m).

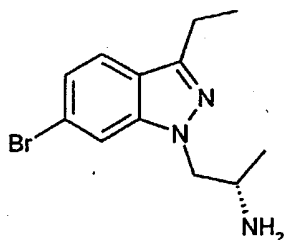
(*S*)-1-(3-Ethyl-6-fluoroindazol-1-yl)-2-propylamine fumarate

10

(*S*)-1-(3-Ethyl-6-fluoroindazol-1-yl)-2-propylamine fumarate was prepared according to the method described in Example 2 using (*S*)-1-[2-(tert-butoxycarbonylamino)propyl]-3-ethyl-6-fluoroindazole (0.9 g, 2.8 mmol) to produce 0.5 g (54% yield) of the title compound as a colourless solid: mp 143-145 °C; IR ν_{\max} (Nujol/cm⁻¹) 1702, 1627, 1461, 1377, 1124, 972, and 652; NMR δ_{H} (400 MHz, DMSO-*d*₆) 1.13 (3H, d, *J* 6.5 Hz), 1.32 (3H, t, *J* 7.5 Hz), 1.43 (2H, q, *J* 7.5 Hz), 3.59 (1H, m), 4.34-4.51 (2H, m), 6.49 (2H, s), 6.95-7.03 (1H, m), 7.56 (1H, dd, *J* 2, 10 Hz) and 7.8 (1H, dd, *J* 5, 8.5 Hz).

Example 7: (*S*)-1-(6-Bromo-3-ethylindazol-1-yl)-2-propylamine fumarate

20



4'-Bromo-2'-fluoropropiophenone

A mixture of 3-fluorobromobenzene (5.0 g, 29 mmol) and aluminium (III) chloride (11.6 g, 87 mmol) was heated under argon until a slurry formed. Propionyl chloride (3.2 g, 35 mmol) was added over 15 min and the mixture was heated at 90 °C for 1 h. The reaction was poured onto ice-water (100 mL) and the resultant mixture was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried

(magnesium sulfate), concentrated *in vacuo* and purified by column chromatography (SiO₂; heptane) to give the product (1.2 g, 18%) as a colourless oil: NMR δ_H (400 MHz, CDCl₃) 1.18 (3H, t, *J* 7.5), 2.95 (2H, m), 7.29-7.38 (2H, m) and 7.75 (1H, t, *J* 8 Hz).

5 4'-Bromo-2'-fluorophenylpropiohydrazone

4'-Bromo-2'-fluorophenylpropiohydrazone was prepared according to the method described in Example 5 using 4'-bromo-2'-fluoropropiophenone (0.67 g, 3.0 mmol) to produce 0.23 g (32%) of the product as a yellow oil: NMR δ_H (400 MHz, CDCl₃) 1.03-10 1.14 (3H, m), 2.47 (0.6H, q, *J* 7.5 Hz), 2.57 (1.4H, q, *J* 7.5), 5.04 (0.6H, br s), 5.49 (1.4H, br s), 7.09 (0.3H, t, *J* 8 Hz), 7.2-7.3 (1.4H, m) and 7.32-7.42 (1.4H, m).

6-Bromo-3-ethylindazole

6-Bromo-3-ethylindazole was prepared according to the method described in Example 5 15 using 4'-bromo-2'-fluorophenylpropiohydrazone (0.6 g, 2.5 mmol) to produce 0.3 g (54%) of the product as a white solid: IR ν_{max} (Nujol/cm⁻¹) 3204, 1616, 1461, 1377, 1340, 1036 and 800; NMR δ_H (400 MHz, CDCl₃) 1.42 (3H, t, *J* 7.5 Hz), 3.01 (2H, q, *J* 7.5 Hz), 7.23-7.27 (1H, m), 7.57 (1H, d, *J* 8.5 Hz) and 7.62 (1H, br s).

20 (S)-6-Bromo-1-[2-(tert-butoxycarbonylamino)propyl]-3-ethylindazole

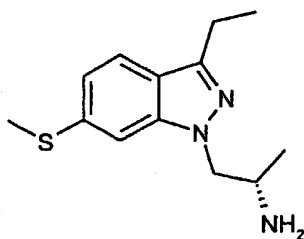
(S)-6-Bromo-1-[2-(tert-butoxycarbonylamino)propyl]-3-ethylindazole was prepared according to the method described in Example 2 using 6-bromo-3-ethylindazole (0.27 g, 1.2 mmol) to produce 0.26 g (61%) of the product as a white solid: IR ν_{max} (Nujol/cm⁻¹) 25 3354, 1681, 1536, 1461, 1371 and 1174; NMR δ_H (400 MHz, CDCl₃) 1.15 (3H, d, *J* 7 Hz), 1.35-1.43 (12H, m), 2.97 (2H, q, *J* 7.5 Hz), 4.03-4.13 (1H, m), 4.31-4.42 (2H, m), 4.79 (1H, br s), 7.20 (1H, dd, *J* 2, 9 Hz), 7.52 (1H, d, *J* 8.5 Hz) and 7.58 (1H, br s).

30 (S)-1-(6-Bromo-3-ethylindazol-1-yl)-2-propylamine fumarate

(S)-1-(6-Bromo-3-ethylindazol-1-yl)-2-propylamine fumarate was prepared according to the method described in Example 2 using (S)-6-bromo-1-[2-(tert-butoxycarbonylamino)propyl]-3-ethylindazole (0.6 g, 1.7 mmol) to produce 0.4 g (61%

yield) of the title compound as a white solid: mp 148-150 °C; IR ν_{\max} (Nujol/cm⁻¹) 1702, 1608, 1460, 1377, 1050, 975 and 651; NMR δ_{H} (400 MHz, CDCl₃) 1.13 (3H, d, *J* 6.5 Hz), 1.32 (3H, t, *J* 7.5 Hz), 2.93 (2H, q, *J* 7.5 Hz), 3.57 (1H, m), 4.35-4.52 (2H, m), 6.49 (2H, s), 7.25 (1H, dd, *J* 1.5, 8.5 Hz), 7.74 (1H, d, *J* 8 Hz) and 8.02 (1H, d, *J* 1.5 Hz).

Example 8: (S)-1-(3-Ethyl-6-methylthioindazol-1-yl)-2-propylamine fumarate



2'-Fluoro-4'-methylthiopropiophenone

To a stirred slurry of aluminium (III) chloride (3.3 g, 25 mmol) in chloroform (20 mL) under Ar at 0 °C was added dropwise over 20 min propionyl chloride (2.5 g, 27 mmol) while the temperature was maintained below 10 °C. To the mixture was added portionwise 3-fluorothioanisole (3.0 g, 21 mmol) such that the temperature remained below 5 °C. The mixture was warmed to room temperature, stirred for 30 min, poured onto ice-water (100 mL) and extracted with chloroform (3 x 50 mL). The combined organic extracts were dried (magnesium sulfate) and concentrated *in vacuo* to give the product (3.8 g, 92%) as a pale yellow oil: NMR δ_{H} (400 MHz, CDCl₃) 1.19 (3H, t, *J* 7 Hz), 2.51 (3H, s), 2.96 (2H, m), 6.92 (1H, dd, *J* 2, 8 Hz), 7.03 (1H, dd, *J* 2, 8 Hz) and 7.82 (1H, t, *J* 8 Hz).

2'-Fluoro-4'-methylthiophenylpropiohydrazone

2'-Fluoro-4'-methylthiophenylpropiohydrazone was prepared according to the method described in Example 5 using 2'-fluoro-4'-methylthiopropiophenone (3.3 g, 17 mmol)

to produce 2.3 g (68%) of the product as a colourless oil: IR ν_{\max} (Nujol/cm⁻¹) 3386, 1486, 1400, 1209, 891 and 818; NMR δ_{H} (400 MHz, CDCl₃) 1.06 (1H, t, *J* 7.5 Hz), 1.12 (2H, t, *J* 7.5 Hz), 2.48 (0.6H, q, *J* 7.5 Hz), 2.58 (1.4H, q, *J* 7.5 Hz), 5.06 (0.5H, br s), 5.45 (1.5 H, br s), 6.89-7.13 (2.3H, m) and 7.38 (0.7 H, t, *J* 8 Hz).

5

3-Ethyl-6-methylthio-1*H*-indazole

3-Ethyl-6-methylthio-1*H*-indazole was prepared according to the method described in Example 5 using 2'-fluoro-4'-methylthiophenylpropiohydrazone (2.0 g, 9.4 mmol) to produce 0.87 g (48%) of the product as a pale orange solid: IR ν_{\max} (Nujol/cm⁻¹) 3169, 1618, 1463, 1300, 1046 and 783; NMR δ_{H} (400 MHz, CDCl₃) 1.44 (3H, t, *J* 7.5 Hz), 2.55 (3H, s), 3.03 (2H, q, *J* 7.5 Hz), 7.08 (1H, d, *J* 8.5), 7.28 (1H, s) and 7.6 (1H, d, *J* 8.5).

15 (S)-1-[2-(tert-Butoxycarbonylamino)propyl]-3-ethyl-6-methylthioindazole

(S)-1-[2-(tert-Butoxycarbonylamino)propyl]-3-ethyl-6-methylthioindazole was prepared according to the method described in Example 2 using 3-ethyl-6-methylthio-1*H*-indazole (0.42 g, 2.2 mmol) to produce 1.1 g (69%) of the product as a white solid: IR ν_{\max} (Nujol/cm⁻¹) 3354, 1681, 1512, 1459, 1368, 1250, 1172 and 786; NMR δ_{H} (400 MHz, CDCl₃) 1.13 (3H, d, *J* 7 Hz), 1.34-1.46 (12H, m), 2.57 (3H, s), 2.95 (2H, q, *J* 7.5), 4.04-4.15 (1H, m), 4.27-4.44 (2H, m), 4.93 (1H, br s), 7.03 (1H, d, *J* 8.5 Hz), 7.28 (1H, br s) and 7.55 (1H, d, *J* 9 Hz).

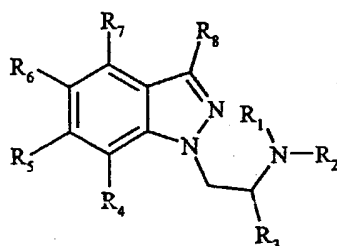
25 (S)-1-(3-Ethyl-6-methylthioindazol-1-yl)-2-propylamine fumarate

(S)-1-(3-Ethyl-6-methylthioindazol-1-yl)-2-propylamine fumarate was prepared according to the method described in Example 2 using (S)-1-[2-(tert-butoxycarbonylamino)propyl]-3-ethyl-6-methylthioindazole (0.45 g, 1.2 mmol) to produce 0.25 g (57% yield) of the title compound as a colourless solid: mp 147-149 °C; IR ν_{\max} (Nujol/cm⁻¹) 1702, 1611, 1460, 1377, 1299, 1224, 971, 798 and 650; NMR δ_{H} (400 MHz, DMSO-*d*₆) 1.13 (3H, d, *J* 6.5 Hz), 1.31 (3H, t, *J* 7.5 Hz), 2.57 (3H, s), 2.89

(2H, q, J 7.5 Hz), 3.59 (1H, m), 4.35-4.56 (2H, m), 6.49 (2H, s), 7.01 (1H, dd, J 1.5, 8.5 Hz), 7.52 (1H, br s) and 7.66 (1H, d, J 8.5 Hz).

CLAIMS

1. A chemical compound of formula (I):



(I)

wherein:

R₁ to R₃ are independently selected from hydrogen and alkyl;

R₄ to R₇ are independently selected from hydrogen, halogen, hydroxy, alkyl, aryl, amino, monoalkylamino, dialkylamino, alkoxy, aryloxy, alkylthio, arylthio, arylsulfoxyl, arylsulfonyl, alkylsulfoxyl, alkylsulfonyl, nitro, cyano, carboxaldehyde, alkylcarbonyl, arylcarbonyl, aminocarbonyl, monoalkylaminocarbonyl, dialkylaminocarbonyl, alkoxycarbonylamino, aminocarbonyloxy, monoalkylaminocarbonyloxy, dialkylaminocarbonyloxy, monoalkylaminocarbonylamino and dialkylaminocarbonylamino; and R₈ is selected from alkyl and alkoxy, and pharmaceutically acceptable salts and prodrugs thereof.

2. A compound according to claim 1 wherein R₁ and R₂ are hydrogen.

3. A compound according to claim 1 wherein R₁ is hydrogen and R₂ is alkyl.

4. A compound according to claim 1 wherein R₁ is hydrogen and R₂ is arylalkyl.

5. A compound according to claim 1, 2, 3 or 4 wherein R₃ is alkyl.

6. A compound according to claim 1, 2, 3 or 4 wherein R₃ is methyl.

7. A compound according to any of claims 1 to 6 wherein one or more of R₄, R₅, R₆ and R₇ is/are hydrogen.
8. A compound according to any of claims 1 to 7 wherein R₄ is hydrogen.
- 5 9. A compound according to any of claims 1 to 8 wherein R₇ is hydrogen.
10. A compound according to any of claims 1 to 7 wherein one or more of R₄ to R₇ is selected from halogen.
- 10 11. A compound according to any of claims 1 to 10 wherein R₅ is halogen, alkoxy or alkylthio.
12. A compound according to any of claims 1 to 11 wherein R₆ is halogen or hydrogen.
- 15 13. A compound according to any of claims 1 to 12 wherein R₈ is alkyl.
14. A compound according to any of claims 1 to 12 wherein R₈ is methyl or ethyl.
- 20 15. A compound according to claim 1 which is selected from 1-(6-methoxy-3-methylindazol-1-yl)-2-propylamine, 1-(5,6-difluoro-3-methylindazol-1-yl)-2-propylamine, 1-(6-chloro-5-fluoro-3-methylindazol-1-yl)-2-propylamine, 1-(3-ethyl-6-trifluoromethylindazol-1-yl)-2-propylamine, 1-(6-bromo-3-ethylindazol-1-yl)-2-propylamine and 1-(3-ethyl-6-methylthioindazol-1-yl)-2-propylamine.
- 25 16. A compound of formula (I) as set out in any one of claims 1 to 15 for use in therapy.
- 30 17. The use of a compound of formula (I) as set out in any of claims 1 to 15 in the manufacture of a medicament for the treatment of disorders of the central nervous system; damage to the central nervous system; cardiovascular disorders; gastrointestinal disorders; diabetes insipidus, and sleep apnea.

- 18 A use according to claim 17 wherein the disorders of the central nervous system
are selected from depression, atypical depression, bipolar disorders, anxiety
disorders, obsessive-compulsive disorders, social phobias or panic states, sleep
5 disorders, sexual dysfunction, psychoses, schizophrenia, migraine and other
conditions associated with cephalic pain or other pain, raised intracranial
pressure, epilepsy, personality disorders, age-related behavioural disorders,
behavioural disorders associated with dementia, organic mental disorders,
mental disorders in childhood, aggressivity, age-related memory disorders,
10 chronic fatigue syndrome, drug and alcohol addiction, obesity, bulimia, anorexia
nervosa and premenstrual tension.
19. A use according to claim 17 wherein the damage to the central nervous system is
by trauma, stroke, neurodegenerative diseases, encephalitis, meningitis or toxic
15 or infective CNS diseases.
20. A use according to claim 19 wherein said toxic or infective CNS disease is
encephalitis or meningitis
- 20 21. A use according to claim 17 wherein the cardiovascular disorder is thrombosis.
22. A use according to claim 17 wherein the gastrointestinal disorder is dysfunction
of gastrointestinal motility.
- 25 23. A use according to claim 17 wherein said medicament is for the treatment of
obesity.
24. A method of treatment of any of the disorders set out in claims 17 to 23
comprising administering to a patient in need of such treatment an effective dose
30 of a compound of formula (I) as set out in any one of claims 1 to 15.
25. A use or method according to any of claims 17 or 24 wherein said treatment is
prophylactic treatment.

26. A method of preparing a compound of formula (I) as set out in any one of claims 1 to 15.
- 5 27. A pharmaceutical composition comprising a compound of formula (I) as set out in any one of claims 1 to 15 in combination with a pharmaceutically acceptable carrier or excipient.
- 10 28. A method of making a composition according to claim 27 comprising combining a compound of formula (I) as set out in any one of claims 1 to 15 with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/GB 99/02875

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/56 A61K31/416 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US HASEGAWA, ATSUSHI ET AL: "Preparation of 3-(piperazinoalkyl)indole derivatives as calmodulin antagonists" retrieved from STN Database accession no. 125:328730 XP002133773 compound with RN=183315-75-5 abstract -& JP 08 225535 A (DAIICHI SEIYAKU CO, JAPAN) 3 September 1996 (1996-09-03)</p> <p style="text-align: center;">— -/-</p>	1, 16, 26-28



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document relating to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

23 March 2000

Date of mailing of the international search report

03/04/2000

Name and mailing address of the ISA

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Authorized officer

De Jong, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02875

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI Section Ch, Week 199011 Derwent Publications Ltd., London, GB; Class B02, AN 1990-079211 XP002133775 -& JP 02 032059 A (KYOWA HAKKO KOGYO KK), 1 February 1990 (1990-02-01) abstract</p>	1,16, 26-28
X	<p>WO 98 30548 A (TSUKAMOTO SHIN ICHI ;KUBOTA HIDEKI (JP); MAENO KYOICHI (JP); SHIMA) 16 July 1998 (1998-07-16) abstract</p>	1,16,17
A	<p>EP 0 469 449 A (NISSHIN FLOUR MILLING CO) 5 February 1992 (1992-02-05) example 19</p>	1,16, 26-28
A	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US ALBERTINI, SILVIO ET AL: "Suppression of mutagenic activity of a series of 5HT_{2c} receptor agonists by the incorporation of a gem-dimethyl group: SAR using the Ames test and a DNA unwinding assay" retrieved from STN Database accession no. 129:226887 XP002133774 compound with RN=176721-37-2 abstract & MUTAGENESIS (1998), 13(4), 397-403 ,</p>	1,16,17
A	<p>EP 0 655 440 A (HOFFMANN LA ROCHE) 31 May 1995 (1995-05-31) cited in the application</p>	1,16, 26-28

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/02875

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 24, 25
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 24, 25
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/02875

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